REMARKS

Applicants respectfully request reconsideration and allowance of the claims, as amended, in light of the remarks made herein. The Examiner is thanked for indicating that claim 3 is allowable. The Examiner is also thanked for courtesies extended during the telephone interview on August 28, 2003.

Claims 1, 3, 4, 6-8, 11-23 and 27, 29-33, 36, 38, 39 and 47 are under examination in this application. Claims 1, 4, 6-8, 11-23, 27, 29-31, 33, 36, 38 and 39 have been amended; claim 47 has been added. Support for each amendment can be found throughout the specification and from the claims as filed. Most of the amendments have been made simply to address formal matters, to correct dependence, and to place the claims in condition for allowance, or at least in better condition for appeal. No new matter has been added.

All of the claims relate to the antibacterial Salivaricin B protein. Claims 1, 3, 4 (independent) and 6 (dependent) are each directed to a protein. Claims 7 and 8 (both dependent) are directed to a composition and therapeutic formulation, respectively, comprising the protein of claims 1, 3, 4 or 6. Claims 10-23 are all dependent claims directed to therapeutic formulations. Claims 27, 29, 30 and 31 are directed to microorganisms. The microorganisms of claims 30 and 31 are bacterial strains that produce Salivaricin B endogenously; the microorganism of claim 27, and dependent claim 29, has been genetically modified to produce the protein, and thus, does not need to be of a particular strain. This embodiment was previously claimed in cancelled claim 28. Dependent claim 32 is directed to a therapeutic composition comprising the microorganism of claim 27, 30 or 31. Claim 33 is a method of treatment claim involving administering one of the claimed proteins, formulations or microorganisms to an individual; and, claims 36, 38 and 39 are method claims that depend from claim 33. Therefore, claims 1, 3, 4, 30 and 31 are the only independent claims pending in this application.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the references cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. §112. The amendments of and additions to the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

Furthermore, it is explicitly stated that the herewith amendments should not give rise to any estoppel, as the herewith amendments are not narrowing amendments.

The Rejections Under §112 Are Overcome

Claims 1, 2, 4-23 and 27-40 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. As was raised in the Amendment filed on March 14, 2003, this rejection is once again presented as an enablement rejection, yet is discussed in terms of what the Applicants possessed, as would apply for a written description rejection. The Office Action states on the top of page 3 that "[t]he rejection is under 35 U.S.C. 112, first paragraph"; however, as was reaffirmed in 1991 by the Federal Circuit in *Vas-Cath, Inc. v. Mahurkar* (935 F.2d 1555,1562, 19 USPQ2d 1111, 1115), the written description requirement is separate and distinct from the enablement requirement. Therefore, Applicants will point out why both written description and enablement exist for the pending claims.

It should be noted that claim 1 no longer recites variants, but instead recites functional and structural features of a protein isolated from a specific strain of bacteria. As such, it is believed that the rejection under 35 U.S.C. §112, first paragraph is moot with respect to claim 1, and the following comments and arguments are made with respect to claim 4 and claims dependent thereon.

The Office Action contends that "[t]here is no evidence on the record that applicant was in clear possession of a protein other than SEQ ID NO:3." This is untrue. The Declaration of Dr. John Tagg, submitted with the March 14, 2003 Amendment ("the first Tagg Declaration), describes a variant of the Salivaricin B protein, isolated from *Streptococcus mitis*. This protein has a histidine, rather than an arginine at position 13, and yet has substantially the same activity profile as the protein of SEQ ID NO:3, as shown in Exhibit 2 of the Declaration.

The Examiner's attention is drawn to Example 14 of the USPTO's "Synopsis of Application of Written Description Guidelines". Example 14 presents a fact pattern that is analogous with that of the instant application. The claim in Example 14 recites the structure of the claimed protein, in the form of a SEQ ID NO and variants with a particular percent identity to the recited sequence, and function in the form of identifying the reaction that the protein catalyzes (i.e. its enzymatic activity). Claim 4 of the instant application recites (1) structure of the claimed protein in the form of a SEQ ID NO, and variants with from one to three amino acid substitutions (i.e. 88-96% identity to the recited sequence), and (2) function of the claimed

protein in the form of its bacteriocidal activity. As discussed in Example 14, even if the claimed SEQ ID NO is the only species disclosed, it is representative of the genus because all members of the genus have the claimed level of identity with and function of the protein described by the reference sequence. In the case of the current application, two members of the genus are disclosed, providing even more evidence than is necessary, according to Example 14 of the Written Description Guidelines, to meet the written description requirement of 35 U.S.C. §112, first paragraph.

With respect to enablement, according to the Court of Appeals for the Federal Circuit in the case of *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988):

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. **The key word is undue, not experimentation.** The determination of what constitutes undue experimentation in a given case requires the application of standard of reasonableness, having due regard for the nature of the invention and the state of the art. **The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed** ... [Emphasis added. Citations omitted].

Id. at 1404.

Against this background, determining whether undue experimentation is required to practice a claimed invention turns on weighing many factors summarized in *In re Wands* (*Id.*), for example, (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims.

Applying *Wands* to the instant facts, enablement is shown to exist. The amount of direction or guidance presented is high; working examples are present; the synthesis of polypeptides and the determination of antibacterial activity is routine; the relative skill of those in the art is high; and the predictability of the art is also high. No evidence to the contrary has been presented.

As stated in MPEP 2164.02, "[p]roof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation." Again, such evidence has not been provided here. In fact, there is no evidence of record that would indicate where the undue experimentation lies. All that is present is a statement on page 3 of the Office Action stating that "[o]ne of ordinary skill in the art would have had no idea which amino acids to substitute, delete, etc.", and this statement is simply untrue. In addition to the example given in the first Tagg Declaration, the paragraph beginning on page 6, line 13, of the specification details potential amino acid substitutions, particularly conservative substitutions.

The invention can be practiced according to the following steps:

1a) Isolate a protein; or

1b) synthesize a protein.

2) Sequence the protein to determine whether it meets the structural requirements recited in the claims.

3) Determine whether the protein is antibacterial and thus meets the functional requirements recited in the claims.

It is unclear which of these steps requires undue experimentation. The specification teaches how to isolate a protein from two strains of *S. salivarius* (step 1a). There is no reason to think that these methods are not applicable to other bacterial strains as well. In fact, the first Tagg Declaration describes the isolation of a Salivaricin B, from *S. mitus*, having one amino acid substitution, as compared with SEQ ID NO;3; and, a second Declaration by Dr. Tagg under 37 C.F.R. §1.132 ("the second Tagg Declaration), attached hereto, attests that the methods taught in the instant application were used to isolate the Salivaricin B variant. Methods of synthesizing (step 1b) and sequencing polypeptides (step 2) are clearly established and well-known to one of skill in the art. The assay described beginning on page 15, line 6, of the specification teaches how to determine whether a protein has bacteriocidal activity (step 3).

Further, the number of variants contemplated by the invention is very small. Indeed, the whole molecule itself is only 25 amino acids in length. Therefore, there are not an infinite number of possibilities for proteins that can fall within the scope of the claims, but rather, there are a calculable number of variants and they can be readily obtained, and their properties

determined, based on the teachings in the application and the knowledge of the skilled artisan at the time of filing.

The second Tagg Declaration provides the expert opinion of one of the inventors, who is obviously of skill in the art, which states that the experiments that would be required to produce, isolate, and/or identify a protein which differs in amino acid sequence from SEQ ID NO:3 by the insertion, deletion or substitution of from one to three amino acids are within the ability of the skilled artisan, and can be achieved without undue experimentation.

Claims 1, 5-23, 27-29 and 33-39 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite.

The word "obtainable" has been replaced with "obtained" in claim 1, obviating the indefiniteness rejection on that basis. The variant and percent identity language has also been removed from claim 1, rendering further discussion with respect to that recitation moot.

In addition, several amendments were made to address improper multiple dependence (claims 9-11, 14, 15, 19, 21, 34 and 38) and antecedent basis (claims 12-14 and 40). Although the claims were not rejected on these bases, such amendments place the claims in better form.

In view of these arguments and amendments, the claims are in compliance with 35 U.S.C. §112; and reconsideration and withdrawal of the rejections thereunder are requested.

The Rejections Under 35 U.S.C. §102 and §103 Are Overcome

Claims 1, 2, 4-15, 21-23 and 27-40 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Caufield *et al.* Claims 1, 2, 4-23 and 27-40 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Caufield *et al.* These rejections are traversed, and will be addressed collectively.

Initially, it should be noted that Caufield *et al.* relates to a protein isolated from *Streptococcus mutans*. Regardless of the difference or similarity of the Caufield sequence to SEQ ID NO:3 (which is discussed in detail below), it is unclear why claims 1 and 29-32 were included in these rejections, as they specifically recite *Streptococcus salivarius*. If this rejection is maintained, it is respectfully requested that the Examiner clarify his reasoning with respect to the inclusion of claims 1 and 29-32 in this rejection.

The Office Action of November 14, 2003 identified the Caufield reference as publishing a sequence that is a 86.9% match to SEQ ID NO:3. Applicants wish, once again, to point out that the match is actually 84%, as is shown in the "best local similarity" field of the computer

readout presented with the Office Action. Applicant have not "decided to create their own system or algorithm", as is alleged in the Office Action. Rather, it is respectfully submitted that Applicants have simply performed straightforward arithmetical calculations: twenty-one of the twenty-five amino acid residues in SEQ ID NO:3 are identical to the sequence of Caufield, as is shown in the computer readout.

$$21/25 \times 100 = 84\%$$

Regardless, claim 4 is directed to a protein whose sequence differs from SEQ ID NO:3 by one to three amino acid insertions, deletions or substitutions. This is not a new recitation; rather, this amendment was made in the Amendment filed on March 14, 2003. Therefore the inclusion of claim 4 in this rejection is misplaced, as is demonstrated in the following discussion. SEQ ID NO:3 and the sequence of Caufield, respectively, are as follows (differences in the Caufield sequence with respect to SEQ ID NO:3 are shown in bold):

```
          5         10        15        20        25
G G G V I Q T I S H E C R M N S W Q F L F T C C S   (SEQ ID NO: 3)
| | | | | | | | | | | | | | | | | | | | | | | |
G S G V I H T I S H E C N M N S W Q F V F T C C S   (Caufield sequence)
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Substitution of Amino Acid Residues

The most straightforward embodiment to consider is the substitution of amino acid residues. Since the substitution of SEQ ID NO:3 by three amino acids is the most dramatic change allowed by the claims, that embodiment will be considered in this discussion. As a comparison of the above sequences demonstrates, even if SEQ ID NO:3 were modified such that there was a Gly→Ser, Gln→His and Arg→Asn substitution at positions 2, 6 and 13, respectively, the result would still not be the sequence of Caufield. (There is still the difference of a Val, rather than a Leu, at position 20.) Therefore, Caufield cannot anticipate the substitution embodiment of claim 4.

Deletion or Insertion of Amino Acid Residues <u>Within</u> SEQ ID NO:3

The next consideration is the deletion or addition of amino acid residues. To consider the instance of internal deletions or additions first, if even one residue is added or deleted anywhere within SEQ ID NO:3, the result will be a shift of the amino acid sequence, such that a shorter length of sequence will be comparable. For example, if amino acid X is added within SEQ ID NO:3, either 6 of the first 8 amino acids are comparable, or 15 of the last 17 are comparable:

G G G V I Q T I X S H E C R M N S W Q F L F T C C S
| | | | | | | | | | | | | | | | | | | | | | | | | |
G S G V I H T I S H E C N M N S W Q F V F T C C S

OR

G G G V I Q T I X S H E C R M N S W Q F L F T C C S
| | | | | | | | | | | | | | | | | | | | | | | | | |
G S G V I H T I S H E C N M N S W Q F V F T C C S

An internal deletion of one amino acid would result in a similar situation. Internal addition or deletion of two or three amino acids, whether consecutive or intermittent, would produce an even more radical difference between the sequences of SEQ ID NO:3 and Caufield.

Deletion or Insertion of Amino Acid Residues At Either End of SEQ ID NO:3

The final possibility is the addition or deletion of consecutive amino acids from either terminus of SEQ ID NO:3. Addition of one to three amino acids to either terminus of SEQ ID NO:3 would do nothing to change the fact that the amino acid residues at positions 2, 6, 13 and 20 are different between SEQ ID NO:3 and the Caufield sequence.

The same is true for deletion of one to three amino acids at the C-terminus or one amino acid at the N-terminus of SEQ ID NO:3. At best, deletion of two or three amino acids at the N-terminus of SEQ ID NO:3 would result in a protein of 23 or 22 amino acids, respectively, three of which differ from the sequence of Caufield. None of the permutations described above is anticipated by Caufield.

Further, there is no disclosure in Caufield *et al.* that could render the instant claims obvious over Caufield, as it neither teaches nor suggests the antibacterial protein of the present invention. There is no evidence of record as to why it would have been obvious to modify the 27 amino acid peptide described by Caufield *et al.* to produce the protein of SEQ ID NO:3 or any claimed variant of it, or that such a protein would be bacteriocidal. In fact, such as suggestion is found nowhere in the Caufield reference.

The Examiner is reminded of the case law, namely, that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious

unless the prior art suggests the desirability of the modification." Also, the Examiner is respectfully reminded that for the §103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988). No such teachings or suggestions are present in Caufield *et al.*, and if such teachings are believed to be present, the Examiner is, once again, respectfully requested to point them out.

Claims 1, 2, 4-23 and 27-40 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Ross *et al.*, Tagg, Sanders *et al.*, Matsushiro or Kawai *et al.* Claims 1, 2, 4-23 and 27-40 were also rejected under 35 U.S.C. §103(a) as allegedly obvious over Ross *et al.*, Tagg, Sanders *et al.*, Matsushiro or Kawai *et al.* taken with Caufield *et al.* These rejections are traversed, and will be treated collectively.

There are several flaws in these rejections. Firstly, it is noted that claim 1 is directed to a protein isolated from strain K12 of *S. salivarius*, and claims 29-32 are directed to cultures of *S. salivarius* strain K12 or K30, therapeutic formulations comprising said cultures, and the organisms themselves. These strains were first identified by the inventors of the instant application, as is confirmed in the second Tagg Declaration. Not one of the cited references teaches, discusses, or even suggests strains K12 or K30 or any proteins isolated from them, because these strains were unknown before being identified by Dr. Tagg and his coworkers. Therefore, no reasonable case has been or could be presented as to why Ross *et al.*, Tagg, Sanders *et al.*, Matsushiro or Kawai *et al.*, alone or in any combination, anticipate or render obvious the subject matter of any of claims 1 or 29-32.

Secondly, none of the references relied upon by the Examiner teach or suggest an isolated antibacterial protein having the sequence of SEQ ID NO:3 or a claimed variant thereof. So even if, as the Examiner argues, the claimed protein is inherent to the microorganisms discussed in the cited references, and Applicants do not admit that they are, an anticipation rejection is improper with respect to claims 1, 3, 4, and claims dependent thereon (i.e. claims 6-8 and 11-23), because these claims are limited to an isolated protein. The isolated protein, as claimed, is not described or suggested in any of the references cited by the Examiner.

Addressing the inherency aspect of the anticipation rejection with respect to Ross *et al.*, Tagg, Sanders *et al.*, Matsushiro and Kawai *et al.*, the Office Action alleges, on page 4, that "[t]he same microorganism is used thus the same protein is obtained." This statement is

incorrect. The organisms described in the instant application are *S. salivarius* strains K12 and K30. Ross relates to *S. salivarius* strain 20P3; Sanders relates to *S. salivarius* strain K58; Matsushiro relates to *S. salivarius* strains M-33 and G8326; and Kawai relates to *S. salivarius* strain ADV10001. The only specific *S. salivarius* strain mentioned in Tagg is Min5. Thus, the same microorganisms are not used in the instant application as in the cited references. And, as is shown in Table 1 of the Tagg reference (cited by the Examiner), and as is emphasized in the first Tagg Declaration, only a small percentage of *S. salivarius* strains tested have been found to produce the claimed protein, Salivaricin B. The Examiner seems to have overlooked the expert declaration in favor of his own opinions.

Furthermore, to establish inherency, the evidence "must make it clear that the missing descriptive matter is **necessarily** present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. **Inherency, however, may not be established by probabilities or possibilities.** The mere fact that a certain thing **may** result from a given set of circumstances is not sufficient." *In re Robertson* 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (emphasis added). *See also* MPEP §2112. There is no evidence to suggest that Salivaricin B is necessarily present in the *S. salivarius* strains mentioned in Ross *et al.*, Tagg, Sanders *et al.*, Matsushiro, Kawai *et al.*, nor is there any reason to believe that, were it present, it would be so recognized by persons of ordinary skill in the art. Therefore, the Examiner has not met the standard prescribed by *In re Robertson* for a rejection based on inherency.

With respect to the obviousness rejection, it is neither taught nor suggested by any of the documents in question that Salivaricin B is produced by any of these organisms. None of the citations teach the production of the protein of the invention, nor has the Examiner established that there would have been any motivation for a person of ordinary skill to make the claimed proteins or variants as presently claimed. There is simply no reason to do so without an appreciation that this 25 amino acid protein is active in its own right, and has distinct bacteriocidal properties.

In view of these arguments, reconsideration and withdrawal of the rejections under 35 U.S.C. §§102 and 103 are requested.

CONCLUSION

Applicants believe that the application is in condition for allowance, and favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. Alternatively, consideration and entry of this paper is requested, as it places this application into better condition for purposes of appeal.

Respectfully submitted,

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